wherein if the level determined in (b) is the same as the level of the fibronectin gene product in said metastatic control, then the human has an increased likelihood of developing a metastatic condition.

41. (New) A method according to Claim 40, wherein the biological sample is a blood sample or a cell sample from a tumor in the mammal.

REMARKS

Amendments to the Specification

The paragraph at page 10, line 24 to page 11, line 6 of the specification has been amended herein to complete the last sentence of the paragraph. Support for this amendment can be found in U.S. Provisional Application Serial No. 60/170,233 filed December 10, 1999 to which the instant application claims the benefit of. The entire teachings of the provisional application were incorporated by reference (see Related Applications, page 1, lines 3-5). No new matter has been added.

The paragraph at page 31, lines 14 through 25 of the specification has been amended herein to correct a minor typographical error. No new matter has been added.

Amendments to the Claims

Claims 12, 14 and 19 have been amended herein. Support for the amendments can be found throughout the specification, for example, at page 10, lines 5 through 9, at page 11, lines 7 through 16, at page 14, lines 22 through 26 and page 30, lines 25 through 27. No new matter has been added.

New Claims 36-41 have been added herein. Support for new Claims 36-41 can be found in the originally filed claims and throughout the specification, for example, at page 11, lines 7 through 16 and at page 14, lines 26 through 29. No new matter has been added.

Information Disclosure Statements

An Information Disclosure Statement (IDS) was filed on June 13, 2001 and a Supplemental Information Disclosure Statement (SIDS) was filed on November 15, 2001.

Applicants note that the Examiner did not initial one reference cited on the PTO-1449 Form accompanying the IDS and did not initial any of the references cited on the PTO-1449 Form accompanying the SIDS. The Examiner stated that copies of the uninitialed references were not provided. Applicants enclose copies of the date-stamped postcard receipts evidencing that the references were sent and received by the United States Patent and Trademark Office. For the Examiner's convenience, Applicants also enclose copies of the references not initialed by the Examiner, along with copies of the previously submitted 1449 Forms. It is requested that the Examiner initial, date and return a copy of the PTO-1449 Forms to indicate consideration of the references enclosed.

Rejection of Claims 12-17, 19 and 27-29 Under 35 U.S.C. §112, First Paragraph

Claims 12-17, 19 and 27-29 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 13, 15, 16, 27 and 28 have been cancelled herein, thus rendering the rejection as it applies to these claims moot. Claims 12, 14 and 29 have been amended to recite methods of predicting the likelihood of development of a metastatic condition in a human.

According to the Examiner's analysis of the factors set forth in *In re Wands*:

> "In view of the breadth of the claims, in view of the limited guidance provided by the specification, in view of the unpredictability of the art, in view of the level of experimentation required, the specification does not describe the claimed invention in such a way as to enable one of skill in the art to make and/or use the invention."

Applicants respectfully disagree. When determining the subject matter encompassed by the claims, the Examiner should interpret what each claim recites and what the subject matter is when the claim is considered as a whole, not when its parts are analyzed individually (see MPEP §2164.08, emphasis in original). Moreover, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (see MPEP §2164.01). The test of enablement is not whether any experimentation is necessary, but whether,

if experimentation is necessary, it is undue. A patent need not teach, and preferably omits, what is well known in the art.

According to the Examiner, the claims are written extremely broad because the exact nature of the likelihood of development of metastasis; the stage of the mammal's life the development occurs; the extent of species metastasis covered; the development of metastasis from a neoplasm of any tissue; the range of biological samples that can be used in testing; and nature of alteration of the cytoskeleton causing metastasis are not described in such a way as to enable on of skill in the art to make and/or use the invention.

Claims 12, 14 and 29, as amended, recite a method of predicting the likelihood of developing a metastatic condition in a human, wherein the level of one or more gene products in a sample as determined in step (b) of the claim is greater than the level of gene product in the non-metastatic control there is an increased likelihood of developing a metastatic condition.

The instant invention is an assay for analyzing the expression levels of one or more gene products which Applicants have discovered to be statistically significant markers for predicting the likelihood of the development of a metastatic condition. As the Examiner has pointed out through Steeg et al. (U.S. Patent No. 5049662), a secondary reference cited in the rejection under 35 U.S.C. 103(a) (see below), one of skill in the art would be able to obtain a sample, determine the level of expression of a gene product in the sample, and compare the expression level of a gene product in a sample to the level of expression of a gene product in a control without undue experimentation. Applicants teach that by looking at the expression levels of specific gene products, e.g., genes which control the actin-based cytoskeleton, wherein if the level of one or more gene products is greater than the level of the gene product(s) in a non-metastatic control, there is an increased likelihood of the development of a metastatic condition. Knowledge of the exact mechanism by which these genes cause or are involved in metastasis is not necessary to practice the claimed invention.

Applicants provide ample teachings throughout the specification wherein the level of one or more identified gene products, which alter the actin-based cytoskeleton, has been shown to be higher in individuals with a metastatic condition than non-metastatic condition. Applicants have examined one stage of neoplasm progression (the development of metastases) and teach that there is an identifiable difference between neoplasms that metastasize and neoplasms that do not.

As such, Applicants teach a correlation between the increased expression of gene products that alter the actin-based cytoskeleton with an increased likelihood of developing a metastatic condition. Thus, Applicants have demonstrated a role for cytoskeletal organization/re-organization in tumor metastasis.

Applicants claim a method and teach what the components of the method are, how the components are measured, and what the result of the method means. The specification and the claims, as amended, enable one of skill in the art to practice the invention without undue experimentation. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 12, 13, 16, 17, 19, 27 and 29 Under 35 U.S.C. §103(a)

Claims 12, 13, 16, 17, 19, 27 and 29 are rejected under 35 U.S.C. §103(a) as being unpatentable over Suwa *et al.* (British J. or Cancer, 77(1): 147-152 (1998))("Suwa") in view of Steeg *et al.* (U.S. Patent No. 5049662)("Steeg").

According to the Examiner, it would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the assay of Suwa in order to form a diagnostic assay as taught by Steeg because of the demonstrated correlation between elevated gene expression and metastatic potential.

Claims 13, 16 and 27 have been cancelled herein, thus rendering the rejection as it applies to these claims moot. Claims 12 and 29 have been amended herein to specify that the gene product which alters the actin-based cytoskeleton is not RhoC. Claims 17 and 19 are dependent on Claim 12.

The Examiner states that Suwa determines the level of gene expression in a biological sample, and correlates the level of expression to an increased likelihood of developing a metastatic condition. Suwa describes that the overexpression of the rhoC gene correlates with progression of ductal adenocarcinoma of the pancreas, and that rhoC RNA levels were significantly higher in tumor portions than in non-malignant portions of the pancreas. Suwa does not disclose any genes other than rhoC, correlate any genes other than rhoC with metastasis or teach that any gene other than rhoC could be used to predict the likelihood of developing a metastatic condition. In fact, although Suwa states that metastatic lesions overexpressed the rhoC gene as compared to primary tumors, this assertion is not supported by the data in Table 2

and in Figure 2 of Suwa. Table 2 shows that the levels of expressed rhoC gene for case numbers 28-33 (cases with metastatic adenocarcinoma) were about the same or lower than cases 1-27 (which were non-metastatic). However, in the interest of expediting prosecution, rhoC has been cancelled from the instant claims as a single predictor for the likelihood of developing a metastatic condition. Thus, Suwa does not teach or suggest the instant invention as claimed.

Steeg does not provide the teaching which Suwa lacks. Steeg describes the identification of the NM23 gene and its use for predicting metastatic potential in animal experimental model systems and human cancer. Steeg goes on to describe that NM23 RNA levels were greatest in cells and tumors of low metastatic potential, and declined in highly metastatic specimens. Steeg does not disclose any genes other than NM23, correlate any genes other than NM23 with metastasis or teach that any gene other than NM23 could be used to predict the likelihood of developing a metastatic condition. Moreover, there is no teaching in Steeg that NM23 is involved with the actin-based cytoskeleton.

The cited references, alone or in combination, do not teach or suggest the methods of the instant claims, as amended. As such, the claimed invention is not obvious over the prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 14 Under 35 U.S.C. §103(a)

Claim 14 is rejected under 35 U.S.C. §103(a) as being unpatentable over Fleischmann *et al.* (The J. of Urology, 149:268-271 (1993))("Fleischmann") in view of Steeg.

According to the Examiner, "the teachings of Fleischmann determine the level of gene expression in a biological sample, and correlate the level of expression to the likelihood of developing a metastatic condition." Thus, according to the Examiner, it would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the assay of Fleischmann in order to form a diagnostic assay as taught by Steeg because of the demonstrated correlation between elevated gene expression and metastatic potential.

The Examiner states that page 269, right column, first paragraph of Fleischmann teaches that if the level of fibronectin expression determined in the biological sample is greater than the level of fibronectin gene product in the control, then the mammal has an increased likelihood of developing a metastatic condition. The Examiner further states that Fleischmann determined that

a decreased level of gene expression correlates with an increased likelihood of developing a metastatic condition.

Applicants respectfully disagree. There are no teachings within the Fleischmann article which support these assertions by the Examiner. The teachings of Fleischmann do not make any connection between the level of fibronectin gene expression and metastases. Rather, Fleischmann only looks at fibronectin expression on the normal mucosa associated with superficial bladder cancer, and at fibronectin's possible role as a marker for predicting the clinical response of surgical specimens to bacillus Calmette-Geurin (BCG) therapy. (see Abstract). Fleischmann states that tumors that showed an unfavorable response to BCG therapy were correlated with a lack of fibronectin expression on the normal mucosa. (page 270, right column, first full paragraph).

Table 1 of Fleischmann shows that 5 tumors developed metastases despite BCG therapy. According to Fleischmann, tumors that failed to respond to BCG therapy lacked fibronectin expression on the normal mucosa. Furthermore, Fleischmann does not teach or suggest that the development of these metastases is correlated in any way with any alteration in the expression of fibronectin. In fact, Fleischmann teaches that basement membrane fibronectin deficiencies alone did not correlate well with tumor progression (see page 269, col. 2, lines 44-46 and Table 3).

Steeg does not provide the teaching which Fleischmann lacks. As discussed above, Steeg describes the identification of the NM23 gene and its use for predicting metastatic potential in animal experimental model systems and human cancer. Steeg goes on to describe that NM23 RNA levels were greatest in cells and tumors of low metastatic potential, and declined in highly metastatic specimens. Steeg does not disclose any genes other than NM23, correlate any genes other than NM23 with metastasis or teach that any gene other than NM23 could be used to predict the likelihood of developing a metastatic condition. Moreover, there is no teaching in Steeg that NM23 is involved with the actin-based cytoskeleton.

The cited references, alone or in combination, do not teach or suggest the method of instant Claim 14, as amended. As such, the claimed invention is not obvious over the prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 15 and 28 Under 35 U.S.C. §103(a)

Claims 15 and 28 are rejected under 35 U.S.C. §103(a) as being unpatentable over Suwa in view of Steeg in further view of Fleischmann.

Claims 15 and 28 have been cancelled herein, thus rendering the rejection moot. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,
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MARKED-UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 10, line 24 through page 11, line 6 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Mammals which can be treated or diagnosed according to methods described herein include, but are not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, guinea pigs, rats, mice or other bovine, ovine, equine, canine, feline, rodent or murine species. A mammal to be treated can be at risk for a metastatic condition, either genetically (e.g., through heredity) or environmentally, or the mammal can have one or more non-metastatic tumors. For example, be administered to a mammal having a metastatic condition to inhibit further metastasis. The [the] mammal may be at risk for or currently have one or more non-metastatic conditions selected from the group consisting of melanoma, breast cancer, ovarian cancer, prostate cancer, lung cancer, bone cancer, throat cancer, brain cancer, testicular cancer, liver cancer, stomach cancer, pancreatic cancer, and combinations thereof. Thus, the described treatment can be administered prophylactically or therapeutically. The described treatment can also be administered to a mammal having a metastatic condition to inhibit further metastasis.

Replace the paragraph at page 31, lines 14 through 25 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Fibronectin is an extracellular glycoprotein that serves as a ligand for the integrin family of cell adhesion receptors. RhoC is a member of the Rho GTPase family that has been shown to regulate numerous cellular functions, most notably cytoskeletal organization in response to extracellular factors (van Aelst and D'souze-Schorey, 1997). Thymosin β4 is an actin-sequestering protein that regulates actin polymerization that has not been directly implicated in metastasis. Other regulators of the cytoskeleton also appear on the list, including ESTs for α-actin 1 and α-centractin,

and α-catenin, an intracellular component of cadherin-mediated cell-cell adhesions. Cadherins are linked to the actin-based cytoskeleton through α-catenin (Ranscht, 1994). The altered expression of so many genes whose products regulate the actin cytoskeleton either directly or indirectly suggests an important role for cytoskeletal organization [organizaiton] in tumor metastasis.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

12. (Amended) A method of predicting the likelihood of development of a metastatic condition in a [mammal] human, comprising the steps of:

a) obtaining a biological sample from a human [mammal] to be tested;

b) determining the level of one or more gene products , excluding RhoC, which alter the actin-based cytoskeleton of one or more tumor cells in the human [mammal]; and

c) comparing the level determined in (b) with a non-metastatic [an appropriate] control,

wherein if the level determined in (b) is greater than the level of the gene product in the non-metastatic control, then the human [mammal] has an increased likelihood of developing a metastatic condition.

14. (Amended) A method of predicting the likelihood of development of a metastatic condition in a [mammal] human, comprising the steps of:

a) obtaining a biological sample from a human [mammal] to be tested;

b) determining the level of one or more gene products selected from the group consisting of fibronectin, [RhoC,] thymosin β4, t-PA, angiopoietin 1, IEX-1/Glu96, RTP/NDR1, fibromodulin, Hsp70, IL13 Rec. α2, Sec61β, snRNP polypeptide C, collagen Iα2, UBE21, KIAA0156, TGFβ superfamily, surfactant protein C, lysozyme M, matrix Gla protein, Tsa-1, collagen IIIα1, biglycan, α-catenin, valosin-containing protein, ERK-1, α-actinin 1, calmodulin, EIF4γ, α-centractin, IQGAP1, cathepsin S, [or] and EF2, in one or more tumor cells in the human [mammal]; and

c) comparing the level determined in (b) with a non-metastatic [an appropriate] control,

wherein if the level determined in (b) is greater than the level of the gene product in the non-metastatic control, then the human [mammal] has an increased likelihood of developing a metastatic condition.

29. (Amended) A method of predicting the likelihood of development of a metastatic condition in a [mammal] human, comprising the steps of:

a) obtaining a biological sample from a human [mammal] to be tested;

b) determining the level of fibronectin [rhoC] gene product in one or more tumor cells in the [mammal] human; and

c) comparing the level determined in (b) with the level of fibronectin [rhoC] gene product in a non-metastatic [an appropriate] control,

wherein if the level determined in (b) is greater than the level of the fibronectin [rhoC] gene product in said non-metastatic control, then the human [mammal] has an increased likelihood of developing a metastatic condition.